REMARKS

Amendments to the Claims

Claims 1-5, 7-25, 27-89 are pending.

Claims 11-20, 31-56, 59, 61-69 and 71-88 have been previously withdrawn from consideration.

Claims 57-58 are being canceled.

Claims 1, 21, 60, 70 and 89 are being amended.

New Claims 90-91 are being added.

Claims 1, 21, 70 and 89 have been amended to delete "locally" to particularly point out the claimed invention. These claims recite administration of a formulation into the bone. Claim 89 has been also amended to delete "systematically" to particularly point out the present invention. Claim 89 has been amended to recite "wherein the second formulation is in the bone in an effective amount for at least one month." Support for this amendment is found, for example, in the Specification at page 16, lines 15-23. Claim 60 has been amended to add recitation of "an anti-resorptive agent." Support for this amendment is found in the Specification at page 54, lines 20-21.

New Claim 90 recites "The method of Claim 1, wherein the bone forming agent is released from a sustained release device." Support for Claim 90 is found, for example, in the Specification at page 40, lines 14-21. New Claim 91 recites "The method of Claim 60, wherein the anti-resorptive agent comprises an anti-TNF-α monoclonal antibody." Support for Claim 91 is found, for example, in the Specification at page 28, line 24 and at page 30, lines 5-23.

No new matter has been added. Entry of these amendments into the application is respectfully requested.

Rejection of Claim 60 Under 35 U.S.C. §103(a)

The Examiner has rejected Claim 60 under 35 U.S.C. §103(a) as being obvious over Trieu *et al.* (US 2002/0026244; hereinafter "Trieu"). Applicants respectfully traverse the rejection.

The Examiner states that "Trieu *et al.* teaches nucleus pulposus implants...The method involves removal of the natural nucleus pulposus of the intravertebral disc and implantation of the nucleus pulposus of the invention (page 10, paragraph [0109])." Further, the Examiner states

that "[t]he nucleus pulposus implant of the invention may contain pharmacological agents used to treat osteoporosis including a bone morphogenetic protein, growth factors such as fibroblast growth factor and platelet-derived growth factor, and steroids (page 9, paragraphs [0101] and [0104])."

Claim 60 has been amended to recite that the device is adapted to deliver an anti-resorptive agent as well as a bone forming agent into the vertebral body.

First, Trieu does not teach all the elements of Claim 60 as amended. Trieu teaches that "[w]hen the implants are formed from an elastic material, such as a hydrogel, or other similar hydrophilic material, or include the resorbable outer shell, they may advantageously deliver desired pharmacological agents" (page 9, paragraph [0101]). Because Trieu's teachings are only applicable to a nucleus pulposus implant, the agents according to the teachings of Trieu are released from a nucleus pulposus implant in the intervertebral disc space. Thus, Trieu does not teach intraosseous implantation of a device into the vertebral body. Further, Trieu does not teach administration of an anti-resorptive agent (ARA) as reflected in the claim as currently amended. Accordingly, a *prima facie* case of obviousness has not been established.

Second, the elements not taught by Trieu, but present in Claim 60, have significant advantages over the teachings of Trieu. The present invention is advantageous over the teachings of Trieu because the device remains within the bone, and the formulations of the present invention are, therefore, administered intraosseously into the osteoporotic vertebral body. The advantages of intraosseous administration can include: reduced time between administration of agents and initiation of bone growth stimulated by the agents; reduced amounts of agents required to achieve desired bone growth (*i.e.*, an increased potency); reduced unwanted side effects caused by the agents outside the bone; and an increased half-life of the formulation in the bone. The Specification of the instant application particularly points out these advantages of intraosseous administration:

> Providing local administration of an osteotherapeutic drug is desirable because the local nature of the injection of the drug will significantly mitigate the risk that the drug will cause unwanted side effects outside of the target bone. Restricting delivery to the local area also allows the drug to be delivered in a higher concentration than would normally be used in a systemic administration, thereby increasing the residence time and the potency of the therapeutic amount of the drug...[S]ince the cortical shell of the bone comprises a relatively dense structure, this outer component of the bone may prevent the out-diffusion of the drug and so

> may provide a suitable depot for the osteotherapeutic drug, thereby increasing its half-life in the target bone. (the Specification at page 7, lines 8-17).

In contrast, because Trieu teaches that the agents are released from the nucleus pulposus implant (*i.e.*, within the intervertebral disc space), the agents, according to Trieu's teachings, must first travel out of the intervertebral disc space. The agents then travel into the vertebral body either through the periosteum (a membranous structure lining the most outer part of the bone) or via the vascular system connected to the inner part of the vertebral body in order to have a therapeutic impact in the osteopenic/osteoporotic vertebral body. Even if the agents successfully travel through the periosteum, they must diffuse into the bone through the cortical shell of the vertebral body. As taught by the instant application, the cortical shell (highly dense outer part of the bone) may function as a diffusion barrier against drugs (see the Specification at page 7, lines 13-17). Therefore, treating an osteopenic/osteoporotic vertebral body by administering the agents from the intervertebral disc space is highly non-specific and may require an increased amount of otherwise unnecessary doses of the formulation to achieve a desired effect, thereby heightening the risks of unwanted side effects. Accordingly, it is a significant advantage to deliver the agent intraosseously, particularly when the target bone is an osteopenic/osteoporotic vertebral body.

Third, osteoporosis involves the progressive resorption of bone which often requires long-term treatment throughout the resorptive process (see the Specification at page 39, line 26). A person of ordinary skill in the art would not look to the teachings of Trieu for treatment of osteoporosis because Trieu is silent on long-term administration of the agent which would effectively prevent further resorption of the osteopenic bone. The Specification of the present application teaches:

> Because the osteoporosis ("OP") involves the progressive resorption of bone in which many factors are involved, in many instances, simply providing a single dose or even a regimen over the space of a few days may not be sufficient to manage the OP...Accordingly, it is desirable for the AR and/or BF agent to remain within the bone as long as possible in a pharmaceutically effective amount. (the Specification at page 39, line 26 through page 40, line 1).

It should be noted that the teachings of Trieu regarding pharmaceutical agents are focused on repairing physical damage to the annulus fibrosis or top and bottom endplates

of the disc (see Trieu page 9, paragraphs [0101] and [0102]). For example, such damage may include a surgical incision made to the annulus fibrosis during the nucleus pulposus implantation procedure. This type of structural damage to the disc can be repaired with a rather short-term treatment by promoting the healing process. In contrast, physical damage produced by the osteopenic/osteoporotic process may take at least 1 month to 6 or 12 months or even longer to be repaired by the restoring of the bone forming process of the uncoupled resorbing bone.

Therefore, it would not have been obvious to a person of ordinary skill in the art to take the teachings of Trieu for treatment of disc damage and apply them to treating the osteoporotic vertebral body by a bone forming agent released within the bone for an extended period of time.

In addition, Applicants have also added new Claim 90, which recites "The method of Claim 1, wherein the bone forming agent is released from a sustained release device." In order to ensure the long-term persistence of the agents within the bone, the Specification of the instant application discloses that:

> The sustained release device is adapted to remain within the bone for a prolonged period and slowly release the BF and/or AR agent contained therein to the surrounding environment. This mode of delivery allows a BF and/or AR agent to remain in therapeutically effective amounts within the bone for a prolonged period. One or more additional therapeutic agents can also be delivered by a sustained delivery device. (the Specification at page 40, lines 16-21).

Reconsideration and withdrawal of the rejections are respectfully requested.

Rejections of Claims 1-10, 21-30, 70 and 89 Under 35 U.S.C. §103(a)

Claims 1-10, 21-30, 70 and 89 are rejected under 35 U.S.C. §103(a) as being unpatentable over Radomsky (U.S. Patent No. 5,942,499; hereinafter "Radomsky") in view of Trieu *et al.* (U.S. 2002/0026244; hereinafter "Trieu") and Boyle *et al.* (U.S. 2003/0207827; hereinafter "Boyle"). Applicants respectfully traverse the rejection.

Radomsky teaches a bone-growth-promoting composition. The composition comprises growth factors such as fibroblast growth factor and platelet-derived growth factor (column 1, lines 19, 35-36, and 61). Radomsky also teaches intraosseous administration of the composition (column 12, lines 5-13).

As discussed above, Trieu teaches nucleus pulposus implants that are resistant to migration. The method involves removal of the natural nucleus pulposus of the intervertebral disc and implantation of the nucleus pulposus implant. Trieu teaches that the nucleus pulposus implants can deliver growth factors which would repair annulus fibrosis and the endplates of the disc (see Trieu, paragraph [0101] and [0102]).

Boyle teaches that osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor (TNFR) superfamily and involved in the regulation of bone formation. Boyle teaches that OPG acts as a soluble receptor of the TNF family and may prevent a receptor-ligand interaction involved in the osteolytic pathway.

The primary reference of record, Radomsky, teaches away from long-term persistence of the formulation taught in the instant application. Radomsky recites that "[i]f the composition persists at the site of desired bone growth for an *excessive period*, its presence at the bone site may inhibit the natural development of the bone, sometimes resulting in no bone formation at all." (Radomsky, column 2, lines 32- 35, *emphasis added*). Radomsky further teaches that "the composition must usually persist at the site of desired bone growth for a period from about three (3) to about thirty (30) days, typically from 3 to about 14 days." (Radomsky, column 2, lines 26-31). Therefore, Radomsky teaches away from intraosseous administration leading to the formulation lasting longer than one month in the bone.

In contrast, the claims are directed to administering the agents into the bone, which, as discussed above, is compatible with long-term persistence of the administered agents in the bone. Further, the claims are directed to treating uncoupled resorbing bone, which often requires such long-term persistence. The instant application teaches that "[b]ecause the osteoporosis ("OP") is progressive resorption of the bone...simply providing a single dose or even a regimen over a few days may not be sufficient to manage the OP." (the Specification at page 39, lines 26-28). It further states that the anti-resorptive and/or bone forming agent is to remain within the bone for as long as possible in a pharmaceutically effective amount (see the Specification at page 39, line 30 through page 40, line 1). It also teaches that "continuous delivery of the AR and/or BF agent is considered to be highly advantageous." (see the Specification at page 40, lines 14-15). The instant application further provides a rationale for the long-term local delivery device by stating that "[s]ince in the case of many BF agents, it may be advantageous to provide an effective amount of the BF agent within the bone for a longer duration, there appears to be a need for a

device that insures the continuous presence of the BF agent for an indefinite period." (the Specification at page 50, lines 7-14, *emphasis added*).

Further, it is well known in the art that osteoporosis progressively develops over at least several years after menopause. Thus, the teachings by Radomsky regarding the short-term presence requirement are largely incompatible with treatment of menopausal osteoporosis in which long-term persistence of the BF and AR agents is desired, as noted above.

Therefore, it would not been obvious to a person of ordinary skill in the art to combine the teachings of Radomsky regarding short-term treatment with those of Trieu and Boyle which are silent on intraosseous treatment and long-term persistence of the agents to arrive at the present claimed invention. Reconsideration and withdrawal of the rejections are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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